REMARKS

I. Status Summary

Claims 7-11, 13, 59, and 101-103 are pending and have been examined in the instant application and have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office").

Claims 7-13 and 59 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification, while enabling for SEQ ID NO: 15, is non-enabling for a polypeptide encoded by a nucleic acid sequence having 65-90% or more sequence identity to the nucleotide sequence of SEQ ID NO: 15 or fragments thereof.

Claims 7 and 59 have been amended. Support for the amendments can be found throughout the specification as filed, including *inter alia* at page 32, lines 6-17 (KCC3a). Additional support can be found at page 71, line 31, through page 72, line 5, and in the Sequence Listing (minimum 90% identity or 95% identity between mouse and human KCC3a, and between different KCC3a nucleic acids and polypeptides, respectively).

New claim 104 has been added. Support for the new claim can be found throughout the specification as filed, including particularly in the Sequence Listing. Additional support can be found on page 6, line 24, through page 7, line 13, and on page 37, line 28, through page 38, line 7.

No new matter has been added with the amendments to the claims or the addition of the new claims. Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Response to the Rejections Under 35 U.S.C. §112, First Paragraph

Claims 7-11, 13, 59, and 101-103 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification, while enabling for SEQ ID NO: 15, is non-enabling for a polypeptide encoded by a nucleic acid sequence having 65-90% or more sequence identity to the nucleotide sequence of SEQ ID NO: 15 or fragments thereof. After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

Applicants respectfully submit that they have disclosed several nucleic acid and polypeptide sequences that correspond to human and murine KCC3a genes and gene products. These sequences are as follows: human and mouse KCC3a cDNA sequences, and the polypeptides encoded thereby (SEQ ID NOs: 15 and 16, and 7 and 8, respectively). Applicants respectfully submit that they have also disclosed splice variants of these human and mouse KCC3a, wherein exon 2 is alternatively spliced during mRNA processing (SEQ ID NOs: 3 and 4, and 5 and 6, respectively). Thus, applicants have identified the following characteristics of the human and mouse KCC3 genes:

1. the KCC3 gene loci in human and in mouse encode at least 3 polypeptides each: KCC3a, KCC3a-X2, and KCC3b
2. KCC3a and KCC3b differ in that each uses a different first exon: exon 1a (SEQ ID NO: 84) or exon 1b (SEQ ID NO: 85)
3. in KCC3a, exon 1a is spliced to exon 2, which is spliced to exon 3, and includes all exons through to exon 25. KCC3b splices from exon 1b, to exon 2, to exon 3, etc., through to exon 25.
4. in KCC3a-X2, exon 2 is removed from the transcript by alternative mRNA splicing, such that exon 1a is spliced to exon 3, which is spliced to exon 4, etc., through to exon 25

Thus, applicants have identified a new genus of potassium-chloride cotransporters: namely, the KCC3a potassium-chloride cotransporters, including the genomic organization of the 25 exons of the relevant human gene (SLC12A6), the nucleotide sequences of the mRNAs, and the amino acid sequences of the encoded polypeptides. Applicants have also discovered that these potassium-chloride cotransporters are all transcribed from mRNAs that include exon 1a and exons 3-25, optionally with exon 2 included. Finally, heterologous expression of human KCC3a, KCC3b, and KCC3a-X2 (referred to in the specification as KCC3a-2m) indicates that all three function as K^+-Cl^- cotransporters in *Xenopus* oocytes.

Turning to the nucleic acid and amino acid sequences themselves, the human and mouse KCC3a cDNAs are 90% identical, and encode polypeptides that are 97% identical.

In support of the instant rejection, the Patent Office asserts:

> The instant Application does not reasonably provide enablement for various protein forms of the KCC3 transporter, wherein the protein sequence is encoded by a nucleic acid that is at least 65-90% identical to the nucleic acid of SEQ ID NO: 15, or to antigenic fragments of SEQ ID NO: 16, or to long fragments with 90% identity to SEQ ID NO: 15. The specification is not enabling for the full scope of the claimed nucleotide, wherein the nucleic acid sequence is 65-90% identical to SEQ ID NO: 15, with the assurance that enabled proteins that are functionally equivalent to SEQ ID NO: 16 can be made without undue experimentation and with the assurance that they would have the desired properties of the claimed KCC3 transporter polynucleotide. There are no examples of what specific polynucleotides fall within the range of those that would be 60-90% identical. Furthermore, since the claims do not specify a function for SEQ ID NO: 16, requiring only that the variants be *biologically active*, the claims embrace numerous polypeptides with unspecified and unknown functions, including those proteins that are structurally dissimilar but serve the same functions within a cell or organism.

Official Action at page 4.

Applicants respectfully traverse the assertions made in the cited paragraph. Initially, applicants respectfully submit that claim 7 has been amended to recite the following: an isolated and purified nucleic acid molecule encoding a biologically active KCC3a potassium-chloride cotransporter polypeptide selected from the group consisting of:

(a) a biologically active KCC3a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO 15;

(b) a biologically active KCC3a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence having 90% or greater sequence identity to SEQ ID NO 15;

(c) a biologically active KCC3a polypeptide having an amino acid sequence as set forth in SEQ ID NO 16; and

(d) a biologically active KCC3a polypeptide comprising an amino acid sequence at least 95% identical to SEQ ID NO: 16,

wherein the biologically active KCC3a polypeptide has potassium-chloride cotransporter activity.

Additionally, applicants have disclosed several other nucleic acid and amino acid sequences of potassium-chloride cotransporters, including SEQ ID NOs: 1-14. As such, applicants respectfully submit that given the disclosure of the various sequences in combination with the discussion presented in the specification with regard to the various domains of the KCC polypeptides generally, one of ordinary skill in the art would not require undue experimentation to produce the nucleic acids and polypeptides recited in claim 7.

The Patent Office also appears to assert that the claimed polypeptides must be functionally identical to the polypeptide of SEQ ID NO: 16. Applicants respectfully submit that the claims include no such requirement. According to the Patent Office,

> As discussed previously (12 December 2003), the selectivity, sensitivity, and activity of the KCC transporters are disclosed as unique for each protein listed...
>
> Furthermore, specific activities of all possible encompassed variants of the protein of SEQ ID NO: 16 and fragments comprising, are not disclosed. Applicants have not produced examples of peptide variants and fragments or a representative number of species of the claimed nucleotide variants and tested them to ensure they were functionally identical to SEQ ID NO: 16.

Official Action at pages 5-6 (emphasis added). Applicants respectfully submit that with regard to the passage cited first immediately hereinabove, even assuming *arguendo* that the selectivity, sensitivity, and activity of the various KCC transporters are unique for each protein listed, the claims are not directed to KCC polypeptides generally. Rather, they are directed to KCC3a polypeptides, and among these, the differences in primary structure solely occur at the N-terminus (*i.e.* the first 90 amino acids of human KCC3a); these alternative isoforms of KCC3 share the same central core of hydrophobic domains, which reside in the plasma membrane and determine the primary transport characteristics (ion specificity, ion affinity, sensitivity to transport inhibitors, etc.). Thus, the differences in the "selectivity, sensitivity, and activity of the KCC transporters" generally is not relevant to the instant rejection of claims 7-11, 13, 59, and 101-103 because these claims specifically recite KCC3a.

Continuing with the instant rejection, the Patent Office asserts:

> Although Applicants have added the phrase "biologically active" to claims in order to ensure that variant transporters have activity, applicant's claims may only encompass a transporter with the specific activity of SEQ ID NO: 16. Applicants have not made and tested all possible variants of SEQ ID NO: 16 that have the same activity of SEQ ID NO: 16. Furthermore, "biologically active" is a very broad functional requirement, encompassing all peptides, for example, that can be fed to animals (because they can be digested providing calories), or all peptides that are immunogenic (which might be true of many or most foreign proteins).

Official Action at page 6. Initially, applicants respectfully submit that claim 7 has been amended to recite that the biological activity is potassium-chloride cotransporter activity. As such, even if the Patent Office's assertion that "biologically active" is a very broad functional term might be technically accurate, applicants respectfully submit that the claim terms must be read in light of the specification, and when this is done, it is clear that applicants intended the "biologically active potassium-chloride cotransporter" to have potassium-chloride cotransporter activity.

Moreover, methods of making modifications of interest are disclosed in the present U.S. patent application. For example, page 44 of the specification refers to "conservative substitutions". Applicants respectfully submit that general sequence modification methods based on conservative substitutions are known in the art. After having done so, applicants respectfully submit that the *Xenopus* oocyte assays disclosed in the instant specification can be used to assay the activities of the various modified KCC3a's. For example, the specification discloses that "[b]iological activity of a potassium chloride cotransporter can be determined, for example, measuring the amount of $^{86}Rb^{+}$ uptake following transformation of the DNA of interest into *Xenopus laevis* oocytes, as disclosed herein". *See* Specification at page 49, lines 6-9. Additionally, Examples 12-16 disclose how to perform this method, and Figures 14-19, among others, presents the results of such analyses.

As a result, applicants respectfully submit that careful consideration of the Wands factors demonstrates that the specification as filed enables claims 7-11, 13, 59, and 101-103. More particularly, (a) the level of skill in the art is high; (b) the specification gives considerable direction and guidance as to how to make and test embodiments of

the claimed subject matter; and (c) the degree of experimentation necessary to prepare new KCC3a's is not undue, considering all of the above.

With regard to the rejection of claim 59 specifically, applicants respectfully submit that this claim has been amended to recite an assay kit for detecting the presence, in biological samples, of a nucleic acid encoding a KCC3a potassium-chloride cotransporter polypeptide, the kit comprising a first container that contains a nucleic acid molecule identical or complementary to a segment of at least ten contiguous nucleotide bases of nucleotides 1-434 of SEQ ID NO: 15. Nucleotides 1-434 of SEQ ID NO: 15 corresponds to the first 434 nucleotides of a human KCC3a cDNA. Thus, applicants respectfully submit that a nucleic acid molecule identical or complementary to a segment of at least ten contiguous nucleotide bases of nucleotides 1-434 of SEQ ID NO: 15 can be used to specifically detect a nucleic acid encoding a KCC3a potassium-chloride cotransporter polypeptide using techniques that are known in the art.

Furthermore, it appears that the instant rejection of claim 59 rested on the enablement rejection applied to claim 7. Applicants respectfully submit that the element reciting "the nucleic acid molecule of claim 7" has been removed, and thus the basis for the instant rejection is believed to have been rendered moot.

Accordingly, applicants respectfully submit that the rejection of claims 7-11, 13, 59, and 101-103 under 35 U.S.C. § 112, first paragraph, has been addressed, and that the claims are in condition for allowance. Applicants respectfully request a Notice of Allowance to that effect.

III. Discussion of the New Claim

New claim 104 has been added. Support for the new claim can be found throughout the specification as filed, including particularly in the Sequence Listing. Additional support can be found on page 6, line 24, through page 7, line 13, and on page 37, line 28, through page 38, line 7. SEQ ID NOs. 3, 5, 7, and 15, and the amino acid sequences encoded thereby (SEQ ID NOs: 4, 6, 8, and 16, respectively), correspond to human and mouse KCC3a gene products. These sequences are all at least 90% identical to each other at the nucleic acid level, and 95% identical to each

other at the amino acid level. Thus, applicants respectfully submit that the species listed in SEQ ID NOs: 3-8, 15, and 16 are all KCC3a gene products.

Applicants respectfully submit that claim 104 is in condition for allowance for the reasons presented hereinabove with regard to claims 7-11, 13, 59, and 101-103, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the subject patent application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Deposit Account

The Commissioner is hereby authorized to charge any deficiencies of payment associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: September 26, 2005 By: _____

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